REMARKS

Claims 1-13 were present in the application as filed. In response to a restriction requirement, Applicants elected the invention of Group I (claims1-12) drawn to a method of treating a subject by administration of Titusville mutant α-globin protein.

Claims 1, 12, and 13 are cancelled. Claims 2-11 are pending. Claim 7 is amended. Applicants have amended the specification to include a cross-reference to related applications. No new matter has been added.

SPECIFICATION OBJECTIONS:

The Office Action has denied Applicants claim to the priority date of March 6, 2003 for failure to provide a certified copy of the foreign document and for failure to provide the priority date in the first paragraph of the specification.

Applicants have included a copy of the foreign priority document and have amended the specification to include a cross-reference to related applications. Withdrawal of this objection is respectfully requested.

CLAIM OBJECTIONS:

The Examiner has rejected claim 7 because the term "modificating of a tissue" is undefined. Applicant has attended to this objection by amending claim 7 and replacing this term with "modification of a tissue." Withdrawal of the objection is respectfully requested.

REJECTION UNDER 35 U.S.C. §102

Rejection of claims 1 and 12 as being anticipated by Hoffman et al.

The Examiner rejected claims 1 and 12 as being anticipated by Hoffman et al. According to the Examiner, Hoffman et al. teaches a pharmaceutical composition of mutant hemoglobins that are useful as substitutes for red blood cells in the delivery of oxygen to tissues, as well as a need for mutant hemoglobins with reduced affinity for oxygen. According to the Examiner, Hoffman et al. further teaches the need for mutant hemoglobins with reduced affinity for oxygen and the use of certain naturally occurring

mutants in the α and β chain of hemoglobin. Hoffman et al. also makes reference to the α-globin Titusville mutation.

Without acceding to the propriety of this rejection, and for the purposes of expediting prosecution of the application, Applicants, have canceled claims 1 and 12. Therefore, this rejection is now moot and withdrawal is respectfully requested.

REJECTION UNDER 35 U.S.C. §103(a)

Rejection of claims 2-4 over Hoffman et al. in view of Standl et al. and Baron et al.

The Examiner has rejected claims 2-4 as being obvious over Hoffman et al. in view of Standl et al. and Baron et al. Specifically, the Examiner asserts that in addition to the application of Hoffman et al. as applied to claims 1 and 12, Standl et al. teaches the use of hemoglobin based oxygen carriers including genetically modified or recombinant hemoglobins produced by various methods and exhibiting superiority over other blood substitutes. Further, according to the Examiner, Baron et al. teaches several hemoglobin based therapeutics now in clinical trials including engineered recombinant alpha subunits. Baron et al. teaches that such hemoglobin therapeutics could provide an immediate onsite replacement for traumatic blood loss and can be used in therapy to prevent ischemia and organ failure.

According to the Examiner, a person of ordinary skill in the art would have a reasonable expectation of success in making and using blood transfusion substitutes of pharmaceutical compositions comprising α-globins in Titusville mutation for ischemia therapy and for enhancing oxygen perfusion tissues experiencing hypoxia.

Claims 2-4 are not obvious under 35 U.S.C. §103(a) over Hoffman et al. in view of Standl et al. and Baron et al. Hoffman et al. teaches pharmaceutical compositions of hemoglobins that are useful substitutes for red blood cells in the delivery of oxygen to tissues. Hoffman et al. makes references to the use of certain naturally occurring mutants of hemoglobin and non-naturally occurring low affinity mutants of hemoglobin. Hoffman et al. mentions the Titusville mutation as well as various other mutants *without* disclosing the advantages of using one particular mutant over another.

Standl et al. teaches chemical modifications of hemoglobins and *does not* teach genetically modified mutant hemoglobins, but only mentions the superiority of chemically modified hemoglobin as oppose to recombinant hemoglobin. Standl et al. is a review article teaching the difficulties and problems associated with the use of modern hemoglobin based oxygen carriers (HBOC) including, vasoconstriction, oxidation of free hemoglobin, immunogenicity or immunosuppression, and disturbance of photometric measurements.

Baron et al. teaches several hemoglobin based therapeutics now in clinical trials. Baron et al. makes mention to "the only recombinant hemoglobin subjected to clinical trials", which Baron et al. states is a modified human hemoglobin tetramer cross-linked with a glycine bridge between the α-subunits. However, the compound being used in the present invention is not a modified tetramer. Further, Baron et al. does not make any mention to naturally occurring mutant hemoglobin.

Applicants discuss the "superior effect of the alleviation of tissue hypoxia" by using Titusville mutant hemoglobin over the Presbyterian mutant hemoglobin. (See page 4 of specification). Applicants have shown that the Titusville type hemoglobin exhibits a superior effect of alleviation of tissue hypoxia as compared the other known mutants, namely the Presbyterian mutant. For instance, with homozygous Titusville mutant mice, the percentage of the Titusville α-globin in all hemoglobin was not more than 15% even at a maximum, while with the Presbyterian mutant mice, the percentage of the Presbyterian type β-globin in all hemoglobin was not more than 30%. (See page 16 of specification). Despite, the lower percentage of Titusville mutant hemoglobin present, Titusville hemoglobin exhibited superior effects as compared to Presbyterian mutant hemoglobin. This surprising and unexpected advantage is indicative of the lack of obviousness of Applicants invention.

No suggestion or motivation to combine the teachings of Hoffman et al. with Standl et al. and Baron exists. Hoffman et al. does not mention the potential superiority of the Titusville mutant over other mutations and Standl et al. only casually mentions recombinant hemoglobin. Standl et al. teaches chemical modification of hemoglobin and does not mention mutant hemoglobins exhibiting a low oxygen affinity that are

genetically modified. Further, Standl et al. only makes a casual reference to recombinant formulations, essentially teaching away from the use of recombinant material. Standl et al. emphasizes that, "...production of the amount of HBOC which would approximately replace the numbers of actually required allogenic RBC units appears to low for recombinant and transgenic formulations." Standl et al. only mentions recombinant hemoglobin as a comparison to chemically modified hemoglobin and touts the advantages of chemically modified hemoglobin over the recombinant counterpart.

Baron et al. only makes a cursory reference to recombinant oxygen-carrying solutions, providing no evidence or discussion on such hemoglobin based carriers. Baron et al. does not mention naturally occurring low affinity mutants.

Since Hoffman does not note any superiority of one mutant over another and Standl et al. only mentions recombinant hemoglobin to demonstrate the superiority of chemically modified hemoglobin, and Baron et al. does not mention low affinity mutants, a person of ordinary skill in the art would not look to Hoffman et al. in view of Standl et al. and Baron et al. for any suggestion or motivation to combine the teachings of these references.

Further, no expectation of success exists. A person of ordinary skill in the art would not find it obvious to use one of the many mutants mentioned in Hoffman et al. with the teachings of Standl et al. when there is no disclosure that a particular mutant may be superior and when Standl et al. only mentions recombinant hemoglobin to distinguish its ability to treat ischemia with chemically modified hemoglobin. Thus, there is no evidence of success for one skilled in the art to rely on.

Therefore, the Applicants respectfully assert that the Examiner has failed to establish a *prima facie* case of obviousness. Consequently, for all of the above reasons, Applicants respectfully submit that clams 2-4 are not obvious.

REJECTION UNDER 35 U.S.C. §103(a)

Rejection of claims 5-10 over Hoffman et al. in view Li et al.

The Examiner has rejected claims 5-10 over Hoffman et al. in view Li et al. Hoffman et al. teaches pharmaceutical compositions of mutant hemoglobins that are

useful as substitutes for red blood cells in the delivery of oxygen to tissues. Li et al. teaches transgenic mice with increased oxygen consumption.

Specifically, the Examiner asserts that it would have been obvious to one of ordinary skill in the art to incorporate the compositions of Titusville mutant hemoglobin as it is naturally modified hemoglobin in a low oxygen affinity state and enhance oxygen consumption, increase oxidative metabolism, increase oxidative enzymatic activity, modify the tissues and enhance the exercise capacity of a subject. Further, according to the Examiner, one of the ordinary skill in the art would have a reasonable expectation of success in making and using blood transfusion substitutes of pharmaceutical compositions comprising alpha globins with Titusville mutation for therapeutic enhancement of tissues.

Claims 5-10 are not obvious under 35 U.S.C. §103(a) over Hoffman et al. in view Li et al. One of ordinary skill in the art would not have been motivation to alter Hoffman et al. in view of Li et al. Li et al. is an irrelevant reference. Li et al. simply discloses transgenic mice with increased oxygen consumption. The transgenic mice generated by Li et al. express a mitochondrial uncoupling protein and there is no mention of mutant hemoglobin, naturally occurring or recombinant. Therefore, there is no suggestion to modify a teaching of using mutant hemoglobin as a substitute for red blood cells to delivery oxygen to tissues with the teachings of enhancing respiration from oxidative phyosphorylation in skeletal muscle to treat obesity and type 2 diabetes.

The Applicants respectfully asserts that the Examiner has failed to establish a *prima facie* case of obviousness. Consequently, for all of the above reasons, Applicants respectfully submit that clams 5-10 are not obvious.

REJECTION UNDER 35 U.S.C. §103(a)

Rejection of claim 11 over Hoffman et al. in view of Abraham et al. and further in view of De la Torre et al.

The Examiner has rejected claim 11 over Hoffman et al. in view of Abraham et al. and further in view of De la Torre et al. Specifically, Hoffman et al. teaches pharmaceutical compositions of mutant hemoglobins that are useful as substitutes for red blood cells in the delivery of oxygen to tissues. According to the Examiner, Abraham et

al. teaches the effect of allosterically modifying hemoglobin towards a low oxygen affinity state in whole blood using modifying drug compounds and that the low oxygen affinity state could be used to treat alzheimers. Further, according to the Examiner, De la Torre et al. teaches that there is now substantial evidence that sporadic alzheimers disease is a vascular disorder caused by vascular dementia. The Examiner concludes that it would have been obvious to one of ordinary skill in the art to incorporate the compositions of Titusville mutant hemoglobin as it is naturally modified in a low oxygen affinity state and to contemplate a method of treating conditions such as cerebro vascular dementia.

The Examiner asserts that the allosteric modification of hemoglobin towards a low oxygen affinity state in whole blood using modifying drug compounds as taught by Abraham et al. is equivalent to having Titusville mutant α-globin proteins that bring down the affinity of hemoglobin for oxygen.

Abraham et al. teaches allosterically modified low affinity hemoglobin. Abraham et al. discoses chemical modifications. A person of ordinary skill in the art recognizes that a chemically modified hemoglobin is quite different from a naturally occurring mutant hemoglobin and that just because an allosteric modified hemoglobin and mutant hemoglobin may result in a decreased oxygen affinity state, a person of ordinary skill in the art would not describe the two as equivalent. Therefore, a person of ordinary skill in the art would not rely on Abraham et al., which teaches chemically modified hemoglobin, to suggest that a naturally occurring mutant hemoglobin would be useful for treating cerebro vascular dementia.

Further, De la Torre et al. teaches that alzheimers disease is a vascular disease, yet there is no mention of hemoglobin, let alone a low affinity mutant hemoglobin. Since De la Torre et al. makes no mention of a low affinity mutant hemoglobin, there is no suggestion to use a mutant hemoglobin to treat alzheimers disease.

Consequently, for all of the above reasons, the Applicants respectfully submit that claim 11 is not obvious, and withdrawal of the rejection is respectfully requested.

CONCLUSION

In view of the above remarks, reconsideration and further examination is respectfully requested.

Applicants have made a diligent effort to place the claims in condition for allowance. However, should there remain unresolved issues that require adverse action, it is respectfully requested that the Examiner telephone Erika J. Senska, Applicants Attorney at (518) 452-5600 so that such issues may be resolved as expeditiously as possible.

For these reasons, and in view of the above amendments, this application is now considered to be in condition for allowance and such action is earnestly solicited.

CERTIFICATE OF MAILING

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Date of Deposit: August 10, 2006

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Respectfully submitted,

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